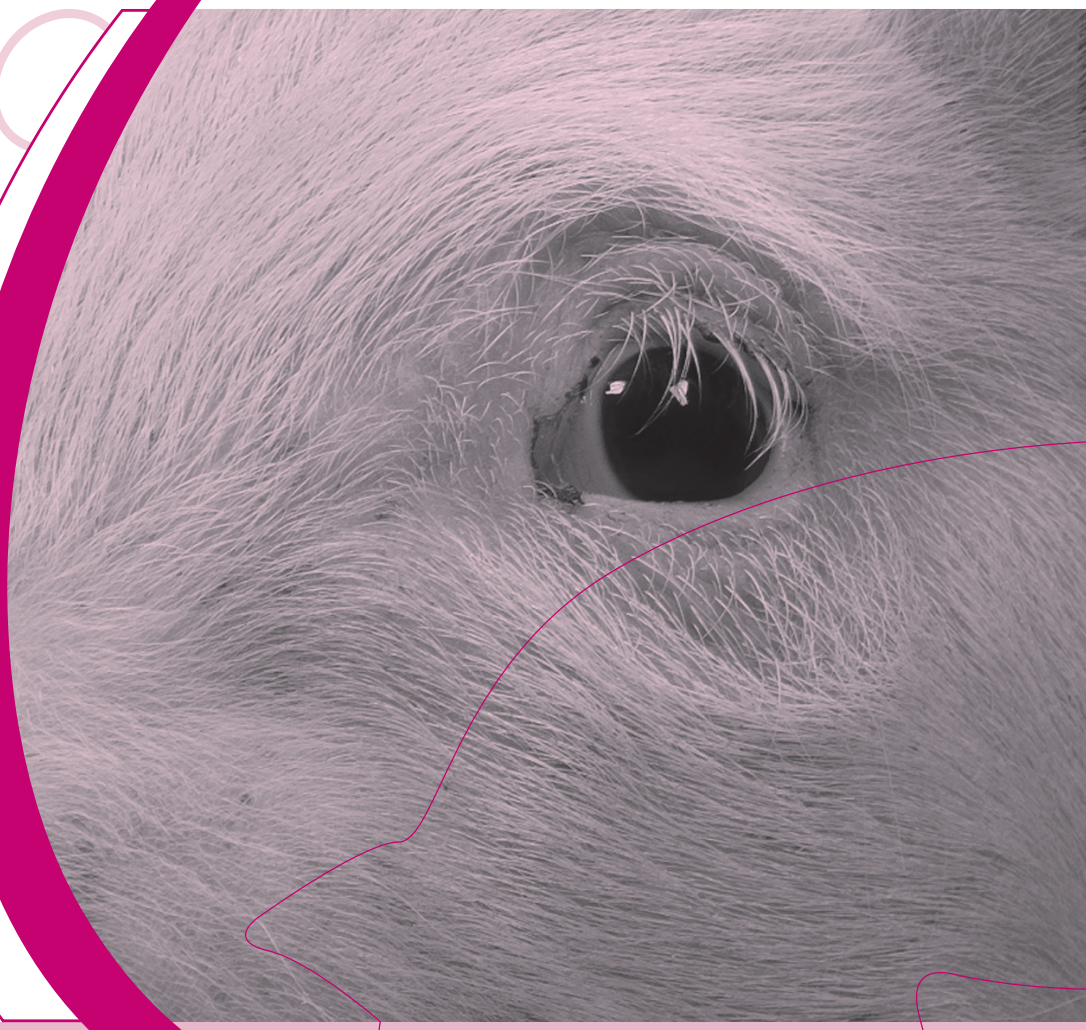
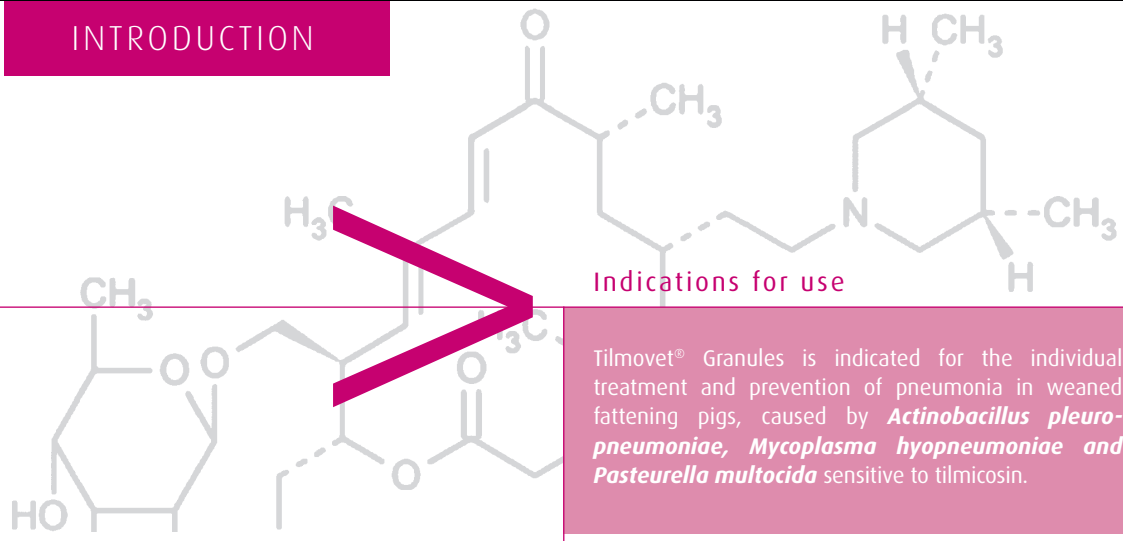
HUVEPHARMA®



Tilmovet® 100 mg/g Granules

FOR INDIVIDUAL TREATMENT

INTRODUCTION



Indications for use

Tilmovet® Granules is indicated for the individual treatment and prevention of pneumonia in weaned fattening pigs, caused by ***Actinobacillus pleuro-pneumoniae, Mycoplasma hyopneumoniae and Pasteurella multocida*** sensitive to tilmicosin.

Origin of the molecule

Tilmovet® Granules contain tilmicosin. It is a semi-synthetic macrolide antibiotic obtained from tylosin which is affecting bacterial protein synthesis. Macrolides have been used for decades as treatment for a wide range of infectious diseases, but their effect on respiratory infections has been getting an increased interest. Tilmovet® is registered exclusively for veterinary use and primarily for acute respiratory diseases like several serotypes of *Actinobacillus pleuropneumoniae* or chronic respiratory diseases like *Mycoplasma hyopneumoniae* and *Pasteurella multocida* and other bacteria sensitive to tilmicosin in pigs, poultry and cattle.

Structure and activity

Tilmicosin has a wide spectrum of activity against Gram-positive organisms of porcine, avian and bovine origin as well as some activity against Gram-negative micro-organisms. Cross-resistance between tilmicosin and other macrolide antibiotics and lincosamides has been observed.

Mode of action

Macrolide antibiotics are bacteriostatic compounds that reversibly bind to NA the 50S ribosome subunit and inhibit mRNA-directed protein synthesis of susceptible micro-organisms. The tilmicosin spectrum of activity includes *Actinobacillus pleuropneumonia, Mycoplasmata, Pasteurella* and Gram-positive bacteria and some Gram-negative germs.

Product categorization and use

Tilmovet® 100 mg/g Granules is an oral granule for individual treatment for pigs. An oral administration of 1 kg of the veterinary medicinal product corresponds to 100 g of tilmicosin active. The dose for pigs is 16 mg tilmicosin per kg of body weight per day for a period of 15 days.
Tilmovet® is also available as oral drinking water solution (specifically suitable for therapeutic use) but also as medicated premix for feeding stuff (ideal to incorporate in therapeutic programs).

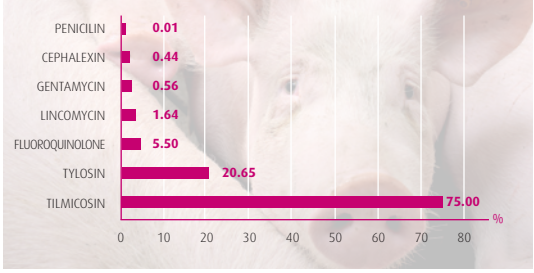
Pharmacokinetic and dynamics

Tilmicosin inhibits the bacterial protein synthesis *in vitro* and *in vivo*, without affecting the nucleic acid synthesis. It is mostly bacteriostatic and has a bactericidal effect on *Pasteurella spp.* Tilmicosin has a wide spectrum of activity against Gram-positive organisms and some Gram-negative micro-organisms, specifically those of the respiratory tract.

Absorption and distribution

When administered to pigs via the oral route at a dose of 16 mg/kg BW in the feed, tilmicosin moves rapidly out of the serum into areas of low pH. Lung concentrations increase rapidly between days 2 and 4. The highest concentration in the serum and maximum concentration in lung tissue are recorded on day 10 of medication.
Apart from high levels in the lungs and lung tissue, high concentrations can be found in lung macrophages (see graph 1: relative concentrations). Tilmicosin is also distributed in the liver and kidney tissues. Due to these high concentrations in swine lung macrophages, it is known that tilmicosin has an indirect antiviral effect on PRRSV in preventing replication of the virus.

Graph 1: Relative Concentration Of Antibiotics In Macrophages In Comparison To Extra Cellular Concentrations.



Tilmicosin: Die Fakten Von Dr. Manfred Stein.
Ref. Scorneaux, B. and Shryock, T.R. 1998, Intracellular accumulation, subcellular distribution and efflux of tilmicosin in swine phagocytes, JVPT 21(4):257-268.

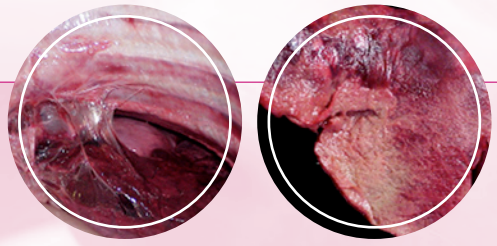
Elimination

Some metabolites are formed, the predominant one being identified as T1. The bulk of tilmicosin is excreted unchanged, although tilmicosin is excreted mainly via the bile into the faeces, but a small proportion is excreted via the urine.

Actinobacillus pleuropneumoniae

Disease

Actinobacillus pleuropneumoniae (APP) is the causative agent of porcine pleuropneumonia, a serious and often fatal disease affecting swine of all ages. All age groups are susceptible, yet in chronically infected herds, pleuropneumonia is mainly diagnosed in fatteners and animals of 12 weeks of age. Pigs can be infected at ages of < 4 weeks, carrying the pathogen in the tonsils without clinical symptoms and without production of antibodies. At older ages, APP can reach the lungs and seroconversion can occur.



Transmission

It is believed that direct contact and nasal droplets within short distance are the main route of disease transmission, although a spread across pens has been seen in acute outbreaks (aerosol transmission, farm personnel).
Susceptible herds are mainly infected by asymptomatically chronically infected animals. Other risk factors are secondary viral and bacterial infections, **stress moments** like weaning, crowding, moving, mixing and adverse climate conditions.

Symptoms

Typical symptoms in (per)acute cases are sudden high fever with apathy, lethargy and anorexia, rapidly followed by cardiac and vascular failure resulting in cyanosis of nose, ear, legs and/or the entire body. Sometimes, diarrhoea and vomiting is observed. In the terminal phase, severe respiratory distress (dyspnoea, coughing, open mouth breathing) can occur.

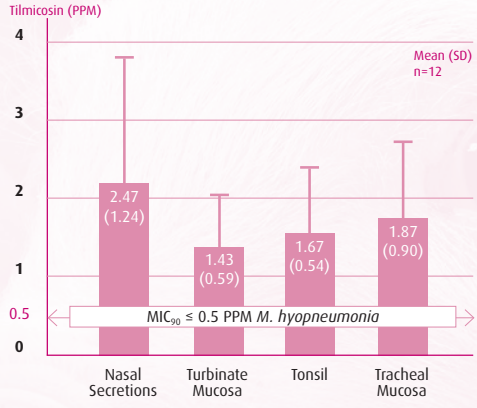
Associated diseases

APP is often complicated with severe PRRS infections. It is assumed that PRRSV infections are triggering APP infections. This combination causes continuous and tremendous losses with mortality rates between 4 and 10%, higher treatment costs in acute outbreaks and an increased feed conversion. Next to this, PRRSV gives rise to a number of reproductive failures (increased abortions, more mummified foetuses, stillborn and weak born piglets).

Interactions with bacteria

The host's defense effectiveness against pulmonary bacterial infections depends on the rapid clearance and its immune reaction and modulation due to direct or indirect antibiotic concentration in different tissues (see graph 3).

Graph 3:
Tilmicosin Concentrations Following *ad lib.* Exposure To Tilmicosin 400 PPM



Fossler, S., JW Moran, TD Thomson., Tilmicosin mode of action against Mycoplasma hyopneumoniae in swine proceedings, 17th IPVS Congress, 2002.

Tilmovet® and pneumonia

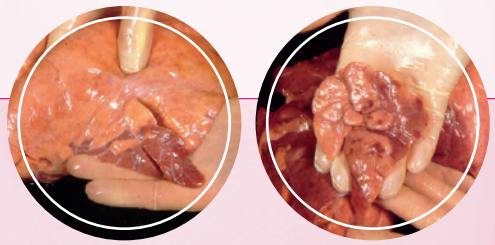
Tilmovet® treatments have a proven beneficial effect on contagious pleuropneumonia. An oral administration decreased the APP pressure in lungs (decreased lung lesions and inflammation) as well as the APP associated mortality. This had a positive impact on daily weight gain, feed conversion and clinical signs in all weight classes. A series of published studies clearly demonstrate that Tilmovet® can perfectly treat clinical outbreaks (reducing clinical signs, mortality and culled pigs) as well as prevent new disease cases. Tilmovet® lowers the possible risk of viral infection by making the macrophage non-permissive.

Macrolides are known to be an effective treatment against pulmonary bacterial infections. In general, this class of product has a series of therapeutic antibacterial effects and concentrates specifically in macrophages, other phagocytic cells, fibroblasts and tracheal and bronchial mucosa.
Tilmicosin was reported to inhibit *in vitro* PRRSV replication in alveolar macrophages. Also, the use of tilmicosin pretreatment of porcine alveolar macrophages significantly reduces replication of PRRSV in a dose dependent way. This results in a significant reduction of lymph node hypertrophy and lung lesions but also a reduced virus load in systemic circulation.

Mycoplasma hyopneumoniae

Disease

Mycoplasma hyopneumoniae is the primary pathogen of enzootic pneumonia. These infections are highly prevalent in almost all swine producing areas, causing significant economic losses due to an increased medication use and decreased performance of the pigs. *M. hyopneumoniae* is considered one of the primary agents involved in the Porcine Respiratory Disease Complex (PRDC). Combined infections with *Pasteurella multocida* and/or *Actinobacillus pleuropneumoniae* result in more severe lesions compared to the single infections. Co- or subsequent infections are commonly found in field outbreaks of enzootic pneumonia.

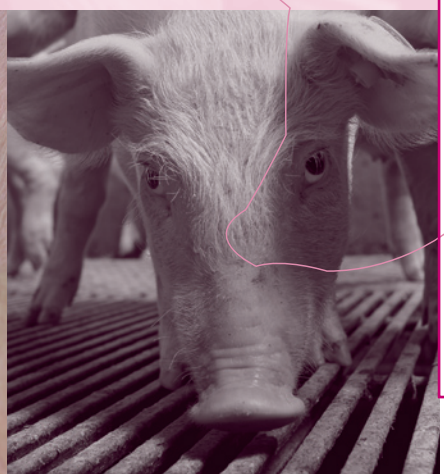


Recommendations for treatment and management of pneumonia

The control of the APP infections requires a combination of management actions, prevention of crowding, mixing and adverse climate stable conditions, treatment and/or vaccination programs.

Tilmicosin is the right antibiotic for:

- Treatment of *Actinobacillus pleuropneumoniae*
- Treatment of *Pasteurella multocida*
- Treatment and managment of *Mycoplasma pneumoniae*.
- Treatment and management of PRDC.



Tilmovet® Granules

Contraindications

Do not use in animals hypersensitive to tilmicosin and when there is resistance to tilmicosin or cross-resistance to other macrolides like tylosin, erythromycin or lincomycin. Also simultaneous use with other macrolides and lincosamides should be avoided.
Never use in horses or other equines and make sure to prevent access to feeds containing tilmicosin. Do not mix into feed containing bentonite and never mix with other veterinary medicinal products.

Special warnings

If for an individual animal, feed intake is such that the recommended dose is not realized, medication should be carried out by parenteral treatment. Occasionally, feed intake may decrease (including feed refusal) in animals receiving medicated feed. This effect is transient.

Special precautions for use in animals

Due to likely variability (time, geographical) in susceptibility of bacteria to Tilmovet® Granules, bacteriological sampling and susceptibility testing is sound clinical practice to decide on the treatment approach. Inappropriate use of the product (i.e. underdosing and/or treating for an insufficient length of time) may increase the prevalence of bacteria resistant to tilmicosin and may decrease the effectiveness of treatment with tilmicosin related substances and should be avoided at all times. Also the sensitivity of bacteria to tilmicosin may have changed over time or geographically.
The product should first be mixed with a suitable quantity of feed before being incorporated into the finished feed. Laboratory studies in rats have not produced any evidence of a teratogenic, foetotoxic/embryotoxic effect of tilmicosin. However, a maternotoxicity was observed at doses that were close to the therapeutic dosage. Tilmovet® Granules can be used safely in sows regardless of pregnancy stage. Nevertheless, a veterinarian must always first be consulted to assess the treatment benefit.

Special precautions for the person administering the veterinary medicinal product to animals

People with known hypersensitivity to tilmicosin should avoid contact with the product. Any skin and ocular contact may cause irritation or sensitization. In case of skin or eye contact, rinse abundantly with fresh water. If irritation persists and in case of accidental ingestion, seek immediate medical advice or call a poison centre (possible dangers linked to disturbances in cardiac conduction). Always wash hands after use.
If the operations involve the risk of exposure to dust, a disposable filter and half mask respirator or a non-disposable respirator fitted with a filter to EN143 should be worn. This warning is particularly relevant to on-farm mixing, where the risk of exposure to dust is likely to be enhanced.

Product specifications

Tilmovet® Granules for medicated feeding stuff has a brownish tan and is characterized by its free-flowing behavior.

Practical use

The use of individual treatment is complementary to that of medicated feed. By nature, medicated feed will have to be used in all animals on a farm, or at least in all animals in a particular stable. This is very efficient when the complete herd is diseased, but is not really practical when only a limited number of animals is affected. In that case an individual treatment via the feed will have a low-stress impact which is efficient, economic and in line with the prudent use of antibiotics. In large scale operations the affected animals will be isolated in separate pens and will receive specific treatment.

Tilmovet® Granules should be administered in small quantities of feed for immediate consumption by individual animals. Pigs to be treated should be separated and treated individually. For treatment of larger groups, it is recommended to use Tilmovet® medicated premix for feeding stuff. To ensure a correct dosage, the body weight should be determined as accurately as possible to avoid underdosing. In case of an altered feed intake (weight class, age, environment) adjust the incorporation in order to guarantee an intake of 16 mg tilmicosin per kg body weight per day.

Tilmovet® 100 mg/g Granules can be mixed thoroughly into a part of the daily feed ration and this can be administered prior to the feeding. It has to be ensured, that the calculated dose is completely taken up by the animals. Consideration must be given to pigs suffering from reduced or restricted daily feed intake.

The required amount of product must be measured by suitably calibrated weighing equipment. The product should only be added to dry non-pelleted feed.

In-use stability

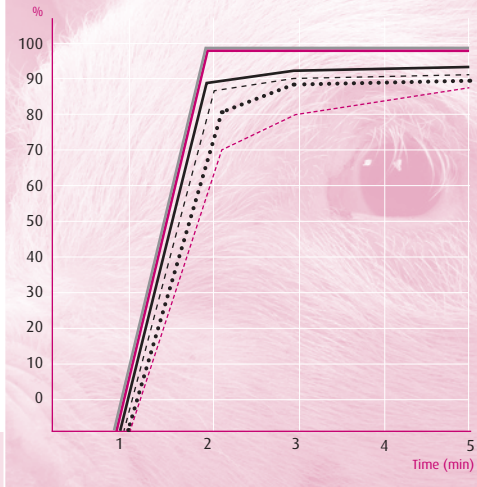
In-use tests after opening of the original bags and under normal environmental conditions for 3 months, demonstrate that the characteristics of the product comply with the specification limits.

- No significant deviations in tilmicosin content and component composition values were found.
- No changes in the impurity profile were observed either.
- In terms of storage conditions, there is no need to take specific precautions, except dry storage in the original packaging.

Dissolution

Several dissolution tests have been performed and these demonstrated that all formulations had an immediate release of the active substance being between 99.34% and 99.9% for the different concentrations. Approximately 95% of the total content in tilmicosin was released in 10 minutes from all the formulations/concentrations. This is well above the dissolution rate of 85% after 15 minutes which is considered enough to guarantee bioavailability.

Graph 2: Comparative Dissolution Test:
Tilmovet® Versus Competing Reference Tilmicosin Formulations



Homogeneity

Homogeneity studies have been performed to verify the homogeneity of the Tilmovet® Granules in mash feed after mixing. All samples showed standard deviations well below 5%, being the maximum percentage of deviation with regard to the mean, thus confirming the homogeneity.

To ensure thorough dispersion of the product, it should first be mixed with a suitable quantity of feed before being incorporated into the feed and it should only be added to dry non-pelleted feed.

Tilmovet® Granules

Amount(s) to be administered and administration route

One kg of Tilmovet® Granules corresponds to 100 g of tilmicosin active. The dose for pigs is 16 mg tilmicosin per kg of body weight for a period of 15 days.

Pigs

- **16 mg tilmicosin, corresponding to 160 mg of Tilmovet® 100 mg/g Granules, per kg BW for a 15 day period.**

Practical administration

The product should be administered to small quantities of feed for immediate consumption by individual animals. For treatment of groups, use an appropriate premix incorporated into medicated feeding stuff. The animals to be treated should be separated and treated individually. The required quantity of product should be thoroughly mixed into the daily ration for each individual pig. The feed containing the granules should be provided as the sole ration for the periods recommended.

The individual pig to be treated should be weighed and the amount of feed that the pig is likely to consume should be estimated. The correct quantity of the product should be added to the estimated quantity of daily ration for each pig, in a bucket or similar receptacle, and thoroughly mixed. The product should only be added to dry non-pelleted feed.

Withdrawal period(s)

Meat and offal

- Pigs: 21 days.

Shelf-life

- Shelf-life of the veterinary medicinal product as packaged for sale: 36 months.
- Shelf-life after first opening the container: 3 months.
- Store in a dry place in the original container.

Incompatibilities

- Do not mix Tilmovet® Granules into feed containing bentonite. Never mix with other veterinary medicinal products.
- Do not use simultaneously with other macrolides and lincosamides.

Packaging

Tilmovet® Granules for medicated feeding stuff has a brownish tan of free-flowing granular material. It is available in a **250 g** or **1 kg bag**. Check with your local Huvepharma representative which pack sizes are available in your region as this may vary.

User warnings:

Because of the possibility of contact dermatitis and irritation of the skin, eyes or respiratory tract, direct contact during administration should be avoided.

Macrolides may induce hypersensitivity reactions (allergy) after injection, inhalation, ingestion or contact with the skin. Cross-hypersensitivity to macrolides may be observed. Allergic reactions to these substances may be particularly hazardous. Therefore, direct contact during administering of the product should be avoided. Hypersensitive persons should avoid all contact with the product. Wear a mask, safety glasses and protective gloves when either reconstituting or administering the solution. After preparation of medicated water, wash exposed skin with soap and water. In case of accidental eye contact, wash the eyes thoroughly with water. Contact a physician immediately if a skin rash is observed, in the event of oedema of the face, lips or eyes, or if breathing difficulties are encountered.

* *Used references can be requested on demand.*
* *Tilmovet® Granules brochure is following the authorized EU SPC (available at request).*
** *Indications listed above are not necessarily authorized in all countries. Please consult the local label for exact indications and posology.*

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